Original Article

INVASIVE ASPERGILLOSIS IN PATIENTS WITH CIRRHOSIS, A CASE REPORT AND REVIEW OF THE LAST 10 YEARS

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ABSTRACT

Background: Untreated invasive aspergillosis (IA) is lethal, yet diagnosis is often delayed. Recognising the risk factors can lead to earlier diagnosis.

We present a case of an invasive pulmonary aspergillosis in a patient with cirrhosis, who had been treated with corticosteroids for 2.5 weeks for alcoholic hepatitis. He was successfully treated with liposomal amphotericin B and caspofungin (first in combination, then caspofungin monotherapy).

Purpose: to evaluate the role of aspergillosis in cirrhosis

Methods: A literature search on aspergillosis in cirrhosis and liver failure patients was conducted in PubMed/Medline (2002-dec 2012), according to pre-set selection criteria.

Results: 20 out of 330 articles were retrieved, representing 43 patients with cirrhosis and/or liver failure who had an aspergillosis infection. Most Aspergillus (A.) infections were due to A. fumigatus and the lungs were the most frequent organ involved (42/43). 58% of the patients used steroids and mortality was 53,5%. The most frequent used antifungal was caspofungin.

Discussion: Diagnosis of IA is difficult and there might be a delay in diagnosis since cirrhosis is not recognised as one of the classical risk factors. Mortality was 53,5%, but this is lower than in previous decades. Since voriconazole is hepatotoxic, treatment with caspofungin and /or amphotericin is preferable.

Conclusion: Early recognition of aspergillosis in a cirrhosis/liver failure patient is crucial and should prompt direct treatment.

Key words: invasive aspergillosis, Cirrhosis, Corticosteroids, Liver failure

INTRODUCTION

Untreated invasive aspergillosis is lethal and early recognition is therefore of vital importance. Known risk factors include prolonged neutropenia, allogenic hematopoietic stem cell and solid organ transplantation. Cirrhosis is not recognised as a classic risk factor and hence diagnosis is often delayed. In the intensive care unit (ICU) however, is cirrhosis, with a duration of stay in the ICU for more then 7 days, already recognised as an intermediate risk factor (1). The specific incidence of aspergillosis in cirrhotic patients is yet unknown. In an older study of patients with acute liver failure, 1/3 had positive yeast/fungal cultures, of which the majority were Candida (C.) albicans (80%), and only 1/16 was an Aspergillus infection (2). In a tertiary centre in China however, 4% of patients, admitted with hepatic failure, had an invasive (probable or proven) aspergillosis (IA) (3). The mortality of IA in patients with acute liver failure or end-stage liver disease, is still high, but has a trend to decline during the recent years, from 87% before 2000 to 61% thereafter (4).

The goal of this article was to evaluate the role of aspergillosis in patients with cirrhosis and/or liver failure, by means of a systematic review. As an illustration, we start by presenting a case of our institution.

CASE REPORT

A 67 year old man, with a history of alcoholic cirrhosis (Child-Pugh classification C (11)), was referred to our clinic, in

February 2011, because of (1) persistent jaundice and liver failure and (2) visualisation of multiple nodular lung lesions. He was recently diagnosed with acute alcoholic hepatitis, for which he received daily methylprednisolone 32 mg for 2.5 weeks.

He presented with a slight cough with yellow/green sputum during the last days, for which amoxicillin/clavulanic acid had been started. He was generally in a poor condition (WHO 3).

The main findings on clinical examination were profound jaundice and bibasal crackles. The laboratory confirmed a total bilirubin of 20 mg/dl (normal value (n): 0,2-1,1), INR of 1,36 (n: 0,9-1,1), albumin 2,4 g/dl (n: 3,4-4,8), platelets 41.000/µl (n: 140.000-362.000), white blood cell count 14.600/µl (n: 4.000-10.000), C-reactive protein of 7.4 mg/dl (n: 0-0.5). Model for end-stage liver disease (MELD) score of 22. On CT thorax there were extensive alveolar consolidations in the lower lobes of the lung, as well as multiple bilateral perihilar solid tissue lesions, with a small central cavitation (Figure 1). Bronchoscopy was performed, which revealed an extensive tracheobronchitis, of which the image was highly suggestive for invasive aspergillosis. Bronchoalveolar lavage (BAL) yields positive cultures for A. fumigatus, as well as C. albicans, while sputum was positive for A. fumigatus and C. non-glabrata. Upon advise of the Infectiology department, a combination of liposomal amphotericin B (5 mg/kg/day, intravenously) and caspofungin (70 mg on the first day and 50 mg intravenously thereafter), was started instead of voriconazole, the recommended first line treatment in guidelines (5), in view of potential hepatotoxicity. Initially the patient responded well, but after 5 days liposomal amphotericin had to be stopped, because of nephrotoxicity. The patient improved and after 6 weeks, the caspofungin was stopped. After 3 months the CT thorax showed a nearly complete resolution of the lesions (Figure 2). After 16 months the patient is still clinically well (apart from an episode of spontaneous bacterial peritonitis) and has no signs of residual aspergillosis infection. There is a favourable evolution of his liver function and ascites has disappeared, MELD score of 13.

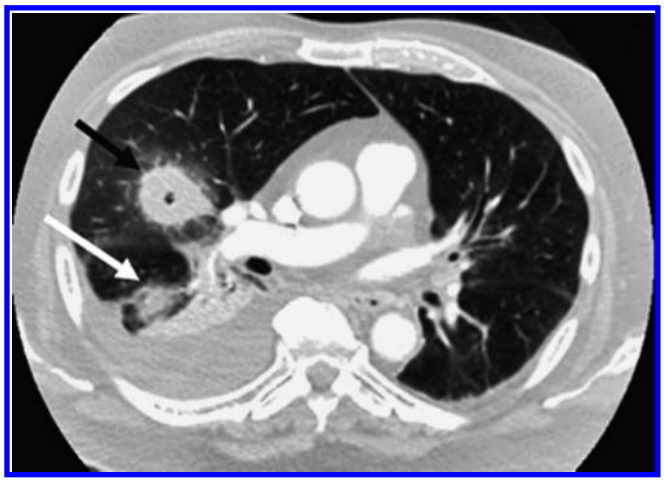

Figure 1: *CT scan showing 2 consolidations in right lung (arrows), one with central cavitation and halo sign (black arrow). Pleural effusion is also seen.*

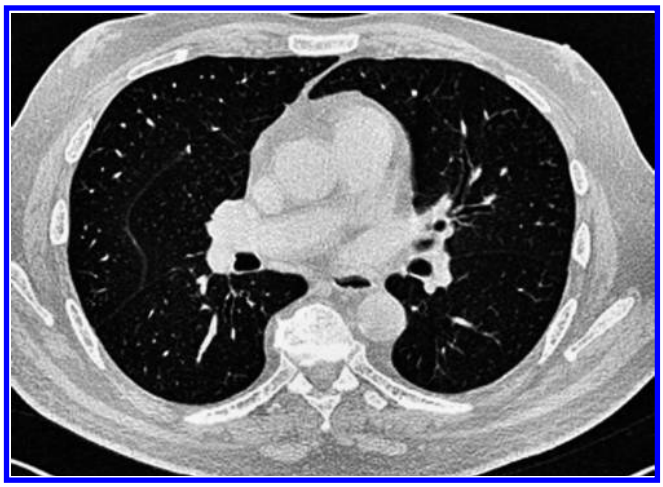

Figure 2: *CT scan after 3 months showing resolution of the lesions.*

METHODS

A literature search on PubMed was conducted, using the following keywords (all Mesh terms): "invasive pulmonary aspergillosis", "Liver cirrhosis AND aspergillosis", "aspergillosis AND liver failure, Acute".

Original articles considering invasive pulmonary aspergillosis (proven or probable infection) in adult patients (16+) with cirrhosis or acute liver failure were selected. Reviews were only included, if they heralded at least one case report, or a series of patients. Expert opinions were excluded. Only articles written in, English, French, German, Spanish or Dutch were accepted. Articles older than ten years were not included, because organisation of hospital care and therapeutic possibilities have changed. Cases on liver transplantation were excluded as well, since this is an entirely different setting.

The last literature search was conducted on the 9th of December 2012.

Definitions for invasive aspergillosis according to the EORTC/MSG Consensus Group (European Organization for Research and Treatment on Cancer/invasive Fungal diseases Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group) were used (6). Definitions can be summarized as follows: infection is '*proven*', when there is histopathological evidence from tissue or culture, obtained from a sterile site (excluding bronchoalveolar lavage (BAL), urine, cranial sinus cavity specimen). Infection is '*probable*' when there is a host risk factor (neutropenia, allogenic stem cell transplant, 0.3 mg/kg/day or prednisone equivalent for > 3 weeks, T cell immunosuppressants or inherited severe immunodeficiency), in combination with clinical features (for invasive fungal infection suggestive lesions on pulmonary HRCT, (i.e. nodular lesions with/without a halo sign, air-crescent sign or cavity), tracheobronchitis, sinonasal infection, or CNS infection) and mycological evidence (positive cultures for Aspergillus species in either sputum, BAL, … and/or antigen detection test, i.e. galactomannan in either plasma or BAL).

RESULTS

A total of 330 articles were found, of which only 20 were retrieved, according to the pre-set selection criteria (Figure 3). Together they represent a total of 45 patients, two of which, could be considered to have a colonisation, they will be excluded from the review, so the total of patients remaining is 43 (3, 4, 7-22). Besides these 43 patients, the article of Wang et al., represents a case-control study of another 43 patients, but since the patients are not dealt with individually, the article is placed at the end of the table and is treated separately. Unless stated otherwise, the following results describe the first 43 patients, excluding those of the case-control study of Wang.

The cases come from 8 different countries, the majority being from Europe (12) and Asia (5) (Table 1).

Patient characteristics

Main causes of liver disease were acute alcoholic hepatitis, alcoholic cirrhosis and liver failure due to hepatitis B or C. Some articles did not specify the etiology of cirrhosis (12, 14-18). Age ranged from 31 to 78 year. According to the EORTC/MSG guidelines, infection with IA is 'proven' in 24/43 (56%) cases, 'probable' in 19/43 (44%). When specified, the most frequent type of Aspergillus is A. fumigatus (16/17 cases) (4, 7-9, 11, 12, 15, 17, 19, 21) followed by A. flavus (1/17) (4). In the case-control study of Wang (22), a different species distribution is observed (A. flavus (58%) and A. fumigatus (42%)). This might be due to epidemiological differences. The most frequent location of IA is the lungs (42/43), except in one case (Choi et al.) where the Aspergillus affected the right ureter. In seven patients other organs were also involved (skin, oesophageal, pericardium, myocardium, stomach, brain, kidneys), with one remarkable patient (7), previously treated with infliximab, azathioprine and high dose corticosteroids, with widely disseminated aspergillosis (lungs, heart, small bowel, stomach, kidneys, brain, pituitary gland, thyroid gland).

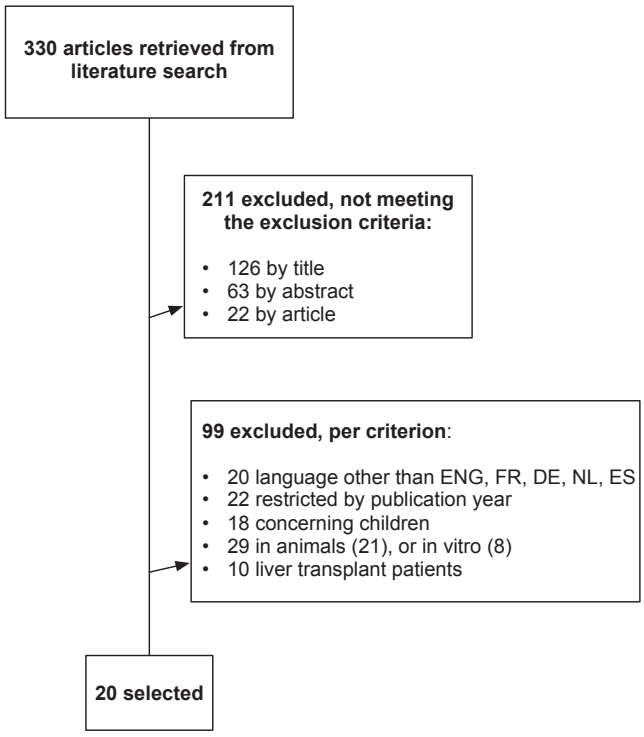

Figure 3: *Selection process.*

Comorbidities/Risk factors

25/43 (58%) of patients used steroids for acute alcoholic hepatitis or for other reasons. A dose of prednisone of 0.3 mg/kg/day for > 3 weeks, is one of the most important host risk factors. Other host factors that predispose to IA, are neutropenia (1/43; 0.02%) and use of nucleoside analogues (cytarabine in one patient). 17/43 (39,5%) had either no host risk factor, or information on it was lacking.

Antibiotics were used in at least 28/43 (65%) of patients. Three patients had chronic obstructive pulmonary disease (COPD) and four had diabetes mellitus, one had cancer (non small lung cell cancer). Sixteen patients had coinfection with other fungi (5/43 or 12%, including Candida albicans, Pneumocystis jiroveci and Mucor mycosis), viruses (4/43; 9%), and/or bacteria (10/43; 23%).

Diagnosis

The signs and symptoms of IA are very nonspecific (17). The most common signs are fever (100%), cough, hemoptysis (91%), and crackles (84%), in the case control study of Wang et al., (22) but in the study of Li et al., (3) 66% of patients did not have any respiratory symptoms at all. Fever is a frequent, but not obligate sign (Sykia et al. (21) presented a case without fever and in the study of Meersseman et al. (17) fever was absent in half of the cases) (data not shown).

Treatment and Prognosis

Mortality in this overview is 53.5% (23/38; five patients had unknown survival status). Only 5 out of 39 did not receive any antifungal treatment (in 4/43 treatment is unknown). Caspofungin was most frequently used (20/39; 51%). We must however stress the fact that the bulk of caspofungin treatments come from the case series of Li (3), from one centre (11 patients received caspofungin in monotherapy). Voriconazole was used in 9 patients (two in combination with caspofungin), amphotericin B in at least 5 (Nam et al. did not specify, treatment per patient, but mentioned it was either amphotericin B or Itraconazole) (1/5 in combination with caspofungin). Itraconazole was used in at least one patient (in second line after voriconazole).

DISCUSSION

To explore the role of IA in cirrhosis/liver failure patients, an overview of the published cases of the last 10 years, was presented. It is remarkable *that cirrhosis is not recognised as a risk factor* according tot the EORTC/MSG, since more than one third of patients didn't had any of the classic risk factors. There is, however a reasonable explanation for cirrhosis being a risk factor for AI, because it is known to negatively affect the immune system (for example by decreased phagocytic capacity of neutrophils, decreased activity of the reticuloendothelial system (bypassing Kupffer cells, reduced number and impaired function of Kupffer cells), decreased T- lymphocyte count, etc.) (23-26). It is probable that cirrhosis itself is an

Table 1: Overview of Case reports

Article			Type of liver disease	Child Pugh score / MELD score*	Steroids**	Other host factors (than steroids)	Comorbidities and immunosuppressive medication	Antiobiotics°	Aspergillus species	Location	Diagnosis∞	Treatment†	Outcome
Alderson et al., 2005 (7) (US)	1	55	hepatitis C cirrhosis	-/15	Y		– infliximab 450mg 1x – azathioprine – Crohn's disease – coinfection with candida, CMV	Y	A. fumigatus	lungs, heart, small bowel, brain, kidneys, stomach, thyroid gland,...	sputum, autopsy (PV)	1) antibiotics 2) fluconazole, 3) AMB 4) voriconazole	died
Alidjinou et al., 2012 (8) (FR)	1	58	Acute alcoholic hepatitis+ hepatitis B cirrhosis	-/-	YU		– history of use of azathioprine and infliximab for Crohn's disease – Non Hodgkin lymphoma coinfection with P. jiroveci, C. albicans	Y	A. fumigatus	lungs	BAL, serum (PB)	1) antibiotics + fluconazole + corticosteroids 2) caspofungin + voriconazole	died
Bienvenu et al., 2010 (9) (FR)	1	50-64	acute alcoholic hepatitis	C/35-48	Y		pneumocystosis	Y	A. fumigatus	lungs	BAL (PB)	caspofungin	died
	2	50-64	acute alcoholic hepatitis	C/35-48	Y		pneumocystosis	Y	A. fumigatus	lungs	BAL (PB)	caspofungin, + L-AMB	died
	3	50-64	acute alcoholic hepatitis	C/35-48	Y		coinfection with pseudomonas aeruginosa, CMV+	Y	A. fumigatus	lungs	BAL (PB)	caspofungin	died
	4	50-64	acute alcoholic hepatitis	C/35-48	Y		coinfection with enterobacter cloacae	Y	A. fumigatus	lungs	BAL (PB)	caspofungin	died
Choi et al., 2011(10) (KR)	1		alcoholic hepatitis	C/-	N		diabetes	N	Not specified	ureteral, later invasive	Pathol.‡ (PV)	1) removal of mass, 2) antibiotics and AMB	died
Delcroix et al., 2006 (11) (BE)	1	31	advanced cirrhosis, toxic or metabolic origine	-/-	YU		hemophagocytic syndrome, tbc, poly-infection (EBV, CMV, Hantovirus, Parvo B19, HS, Mycoplasma pneumoniae, mumps)	Y	A. fumigatus	lung, oesophageal, pericardial	BAL, pericardial fluid (PV)	1) Esomeprazole, diflucan 2) Voriconazole + tuberculostatics + biclar + cymevene 3) switch to caspofungin (after hepatotoxicity to voriconazole)	died
Dimoupolus, et al. 2003 (12)(BE)	1	52	cirrhosis		YU		COPD	U	A. fumigatus	lungs, myocardium, stomach	BAL, sputum, autopsy (PV)	fluconazole	died
Falcone et al., 2011 (4) (IT)	1	78	HCV cirrhosis	C/-	YU¶		COPD, diabetes	Y	A. fumigatus	lungs	sputum, BAL, autopsy (PV)	1) imipenen + linezolid 2) voriconazole	died
	2	51	acute alcoholic hepatitis	-/-	Y		(smoker, homeless)	Y	A. flavus	lungs	Sputum, autopsy (PV)	1) meropenem and levofloxacin, 2) vancomycin added 3) L-AMB	died

Feng et al., 2008 (13) (CN)	1	34	chronic fulminant hepatits B	-/-	Y	–	Y	Not specified	lungs	sputum culture (PB)	1) voriconazole +antibiotics 2) thoracoscopic surgery + itraconzole	survived
Kaiser et al., 2009 (14) (CH)	1	70	cirrhosis	-/-	N	COPD, diabetes	Y	Not specified	lungs, brain	Autopsy (PV)	antibiotics	died
	2	41	hepatitis C cirrhosis	-/-	Y	metastatic NSCLC	N	Not specified	lungs, brain, kidneys	Autopsy (PV)	palliative care	died
Li et al., 2008 (3) (CN)	1	Mean 42	HBV, LF	-/37	9/12		Y	Not specified	lungs (1/12 also in brain)	Biopsy (PV)	caspofungin	survived
	2		HBV,LF	-/29	9/12		Y	Not specified		Biopsy (PV)	caspofungin	survived
	3		HBV, LF	-/32	9/12		Y	Not specified		Biopsy (PV)	caspofungin	survived
	4		HBV, LF	-/33	9/12		Y	Not specified		Biopsy (PV)	caspofungin	survived
	5		HBV and HDV, LF	-/35	9/12		Y	Not specified		Biopsy (PV)	caspofungin	survived
	6		HBV, LF		9/12		Y	Not specified		Biopsy (PV)	caspofungin	survived
	7		HBV, LF	-/39	9/12		Y	Not specified		Biopsy (PV)	none	died
	8		HBV, LF	-/33	9/12		Y	Not specified		Biopsy (PV)	caspofungin	survived
	9		HBV, LF	-/31	9/12		Y	Not specified		Biopsy (PV)	caspofungin	survived
	10		HBV, LF	-/(22-51)	9/12	coinfection with Enterococcus faecium	Y	Not specified		probable	caspofungin	survived
	11		HBV, LF	-/(22-51)	9/12	CMV	Y	Not specified		probable	caspofungin	survived
	12		HBV, LF	-/(22-51)	9/12	coinfection with Mucor mycosis	Y	Not specified		probable	caspofungin	survived
Lipke et al., 2007 (15) (US)	1	52	Cirrhosis (+HCC)	B/-	N	coinfection Pseudomonas aeruginosa	N	A. fumigatus	angioinvasive, disseminated	Autopsy (PV)	piperacilline/ tazobactam + levofloxacin	died
Meersseman et al., 2004 (17) (BE)	1	mean 55	alcoholic cirrhosis	C/-	N		U	A. fumigatus		Autopsy (PV)	?	died
	2	mean 55	alcoholic cirrhosis	C/-	N	peritonitis with E.Coli	U	A. fumigatus		Autopsy (PV)	?	died
	3	mean 55	alcoholic cirrhosis	C/-	N	pneumococcal pneumonia	U	A. fumigatus		autopsy +culture (PV)	?	died
Meersseman et al., 2008 (16) (BE)	1	67	cirrhosis	-/-	N	Peritonitis	U	Not specified	lungs	BAL + biopsy (PV)	AMB	survived
	2	61	cirrhosis	-/-	N	Peritonitis	U	Not specified	lungs	BAL +autopsy (PV)	caspofungin	died
	3	60	cirrhosis	-/-	N		U	Not specified	lungs	BAL +autopsy (PV)	none	died
	4	?	cirrhosis	-/-	U		U	Not specified		Probable (PB)	?	?
Nam et al., 2009 (18) (KR)	total of 4		cirrhosis	?	U	?	U	A. fumigatus, A. flavus, or A. niger	lungs	Serum (PB)	antifungal therapy not specified per patient (itraconazole or AMB)	?
Prodranovic et al., 2007 (19) (FR)	1	54	acute alcoholic hepatitis + cirrhosis	C/-	Y		Y	Not specified	lungs	Serum (GM) (BAL negative) (PB)	1) piperacillin-tazobactam and ofloxacin 2) adding fluconazole 3) switch voriconazole	died
	2	55	alcoholic cirrhosis	C/-	Y	coinfection with S. pneumoniae, S. Aureus	Y	A. fumigatus	lungs	BAL (PB)	1) piperacillin-tazobactam+ofloxacin 2) switch amoxicillin 6g 3) voriconazole	died
	3	64	alcoholic hepatitis + cirrhosis	C/-	YU	Urinary tract infection with Klebsiella	Y	A. fumigatus	lungs	BAL (PB)	voriconazole	died

Article			Type of liver disease	Child Pugh score / MELD score*	Steroids**	Other host factors (than steroids)	Comorbidities and immunosuppressive medication	Antiobiotics°	Aspergillus species	Location	Diagnosis°°	Treatment†	Outcome
Spriet et al., 2011 (20) (BE)	1	53	Alcoholic cirrhosis	B9/-	N	***	AML-M2, bacterial peritonitis	Y	Not specified	lungs	serum Asp Ag (PB)	1) Meropenem, 2) caspofungin	survived
Sykia et al., 2009 (21) (GR)	1	60	chronic HCV cirrhosis	12/-	Y		IFN-α, autoiummune hemolytic anemia, diabetes	Y	A. fumigatus	lungs	Sputum (PB)	Voriconazole +caspofungin	survived
Case control study													
Wang et al. , 2011(22) (CN)	43 pts	mean 48	HBV related liver failure	-/Mean 35	YU (35%)				A. flavus (58%) and A. fumigatus (42%)	lungs	sputum	caspofungin (% of pts?)	died (all)

° Previous or concomitant antibiotics: Y= yes, N= No, U= unknown

°° PV, PB, PS and CZ= respectively Proven, Probable and Possible Invasive Fungal Disease, according to EORTC/MSG, CZ = colonisation

* before "/" Child Pugh Classification score and after "/" MELD score (= Model of End Stage Liver Disease)

** corticosteroids were converted to the equivalent dose of prednisone, if the dose is more or equal to 0,3 mg/kg/day, it is marked in the table as 'Y' (yes), when dose is not stated, but the patient received corticosteroids, it is marked with 'YU' (Yes, but dose Unknown), 'N'= no previous corticosteroids, 'U'= unknown

*** high dose cytarabine and neutropenia

† treatment is in chronological order

‡ Pathol. Pathological examination of resected mass;

¶ corticosteroid inhalation (fluticasone)

Abbreviations: pt= patient number, HBV= hepatitis B virus, HCV= hepatitis C virus, HDV= hepatitis Delta virus, LF= liver failure, ICU: Intensive care unit, COPD: chronic obstructive pulmonary disease, L-AMB: liposomal Amphotericin B, AMB= Amphotericin B deoxycholate, HCC= hepatocellular carcinoma, CMV= cytomegalovirus, BAL= broncho-alveolar fluid, GM: Galactomannan.

independent host risk factor to IA, which has already been suggested before (2, 15, 17, 19). Not considering cirrhosis/liver failure as a risk factor might lead to a delay in diagnosis and treatment, and therefore, a worse prognosis for the patient.

In the overview of cases, other host factors where noted as well, the question is to what degree they add to each other, for example, there was frequent use of steroids (58%). Furthermore, there were 3 COPD patients, which might be an 'at-risk' population as well, especially when treated regularly with corticosteroids, but it has not yet been recognised as an official host factor by the EORTC (12, 27, 28).

In this overview, we registered a *mortality* of 53,5%. In another review mortality was similar (58-61%) for the last 10 years, but higher in the decades before ('73-'99) (4). It should be noted that a lot of survivors came from the study of Li et al. (3), but this is not an ICU department, and patients might have had a better medical condition to start with. Furthermore in the other cases, there are sometimes contributing factors that indicate a worse prognosis (for example concomitant infections, COPD, use of steroids and other immunosuppressants). To better estimate the survival rate of patients with IA and cirrhosis, more prospective studies are needed. We must bear in mind, that acute liver failure in itself carries a poor prognosis (29).

Diagnosis of IA is difficult since the presentation is aspecific. Fungal pneumonia was the most important missed diagnosis in a post-mortem analysis of ICU-patients (30). For the diagnosis of a probable infection, the EORTC/MSG accept the detection of galactomannan (GM) antigen in plasma, serum, BAL or cerebrospinal fluid, as an indirect mycological criterion. GM is a cell wall component of most Aspergillus species. The mean sensitivity for the serum GM is 69% (95% CI, 0,59-0,79), and the mean specificity 0, 89 (95% CI, 0,84 - 0, 94), but there is a great variability between studies and sensitivity drops to 22% in solid organ transplant patients (31). It is known to be of limited value in non-neutropenic patients, since the neutrophils clear GM from circulation (32). The use of antifungals and certain antibiotics (such as piperacillin-tazobactam), further compromise the use of the test (33). Since the EORTC/MSG criteria are not always suitable to diagnose AI in everyday practice, Blot et al. made a clinical algorithm to discriminate colonization from "putative" infection. Several clinical signs are taken into account, as well as any abnormal chest imaging (instead of just the halo- or air-crescent sign or cavity). Moreover the host criteria are less strict and one can lack a host criterion if they have a semi quantitative Aspergillus-positive culture of BAL-fluid, without bacterial growth, together with a positive cytological smear showing branching hyphae. However the algorithm is meant for ICU patients, who have an Aspergillus-positive lower respiratory tract specimen culture (34).

Standard *treatment* of IA, according to the Infectious Diseases Society of America (IDSA) is voriconazole (5). However since voriconazole is hepatotoxic, it should be carefully used in patients with advanced liver failure. The most frequently used antifungal in this overview is the echinocandin, caspofungin (standard dose: 70 mg loading dose on day 1, followed by 50 mg daily). Our own patient was treated with a combination of caspofungin and liposomal amphotericin B. Caspofungin has a different mechanism of action (inhibition of the fungal cell wall polysaccharide 1,3-β-glucan), than amphotericin (binds ergosterol, in fungal cell membrane), and therefore, there remains the potential to use combination therapy. However IDSA does not recommend combination therapy as routine primary treatment, although the committee recognises that a combination of antifungal drugs from different classes can be used as salvage treatment. Ruiz-Camps (35) made an overview of international guidelines and concluded that, although there is insufficient evidence, the combination therapy (voriconazole or caspofungin, with amphotericin B), can be recommend in certain patients.

IDSA recommends a dose reduction of caspofungin in patients with markedly reduced liver function (35 mg daily) (5), however we learned from the study on pharmacokinetics of Spriet et al. (20), that there is no accumulation of caspofungin metabolites. Thus, dose reduction (to 35 mg) might lead to under dosage in a potentially life threatening infection with the need for rapidly effective therapy with the current recommendation for dose reduction to 50 mg, after the loading dose of 70 mg. There is no well defined guideline considering duration of treatment, but a treatment duration of at least 6-12 weeks is recommended, guided by serial evaluation of clinical and radiological signs (without guidance on the interval between assessment points) (5).

Limitations of this article are the heterogeneity of the patient population (ICU patients, as well as ward patients, different comorbidities, etc.) and that it is a retrospective overview, and there might be a bias in reporting (for example tendency to report good outcome-cases). Furthermore, not all relevant data were available for comparison, for example some articles did not report survival status, type of Aspergillus, etc., and it was nearly impossible to compare clinical signs and symptoms, because of the heterogeneity of reporting, if at all.

For future studies, it would be interesting to have a prospective multicentre registration system, to register all new cases of AI in cirrhosis patients, and follow their clinical evolution, treatment and eventual outcome. Moreover it would be interesting to have studies on the pathophysiology of AI in liver cirrhosis. It is known that in neutropenic patients, it is the lack of neutrophils that permits uncontrolled growth of the Aspergillus, whereas in nonneutropenic patients, for example, those treated with corticosteroids, it is the exacerbated inflammatory response that leads to a fatal outcome (36).

Conclusion

Invasive aspergillosis usually presents in patients who are severely immunocompromised, yet in recent years, several non-classic risk groups for IA have been identified, with only minor or moderate immunosuppression. Patients with liver cirrhosis or acute liver failure, fall into this category, and hence there might be a delay in diagnosis. It is therefore important to maintain a high degree of suspicion for IA in these patients, in the presence of suggestive clinical/radiological signs, or absence of response to seemingly appropriate antibiotic therapy. Early appropriate antifungal treatment is imperative to achieve a better survival rate.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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